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Impact of Preoperative FFR on Arterial Bypass Graft Anastomotic Function: the IMPAG trial.

Glineur D^(1,2), Grau J⁽¹⁾, Etienne PY⁽²⁾, Benedetto U⁽³⁾, Fortier J⁽¹⁾, Papadatos S⁽²⁾, Laruelle C⁽²⁾, Pieters D⁽²⁾, El Khoury E⁽²⁾, Blouard P⁽²⁾, Timmermans P⁽²⁾, Ruel M⁽¹⁾, Chong AY⁽¹⁾, So D⁽¹⁾, Chan V⁽¹⁾, Rubens F⁽¹⁾, Gaudino M⁽³⁾.

1) Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, Canada

2) Department of Cardiovascular Medicine and Surgery, Cliniques St Luc, Bouge, Belgium

3) Department of Cardiothoracic Surgery, New York Presbyterian-Weill Cornell Medicine, New York, USA.

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Address for correspondence:

David Glineur, MD PhD

Division of Cardiac Surgery, University of Ottawa Heart Institute, Ottawa, Canada

Tel: +1 6137615312, Email: dglineur@ottawaheart.ca

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Abstract

Aim

Visual estimation is the most commonly used method to evaluate the degree of coronary artery stenosis prior to coronary artery bypass grafting. In interventional cardiology, the use of fractional flow reserve (FFR) to guide revascularization decisions has become routine. We investigated whether the preoperative FFR measurement of coronary lesions is associated with anastomosis graft ~~function~~ flow rate (functionality) 6 months after surgical revascularization using a multiarterial grafting strategy.

Methods and Results

In this prospective double blind study, 67 patients were enrolled from two institutions In Europe and Canada. From these patients, 199 coronary lesions were assessed visually and with FFR at the time of the preoperative angiogram. Patients received coronary revascularization using multiple arterial grafts. A postoperative 6-month angiogram was performed to assess the functionality of the bypass grafts anastomoses. The primary outcome was the association between pre-operative FFR values and anastomotic graft functionality 6 months after surgery.

Preoperative FFR was significantly associated with 6-months anastomotic ~~flow rate~~ function for all conduits and for all targets ($p < 0.001$). An FFR value of ≤ 0.78 was associated with an anastomotic occlusion rate of 3%.

Conclusion

We found a significant association between the preoperative FFR measurement of the target vessel and the 6 months anastomosis functionality, with a cutoff of ≤ 0.78 . Integration of FFR measurement into the pre-operative diagnostic workup before multiarterial coronary surgical revascularization lead to improved anastomotic graft ~~flow rate~~ function.

Introduction

The objective of surgical coronary revascularization is to restore blood supply to a myocardial territory that is ischemic or at risk of infarction through the interposition of a low-resistance conduit to the diseased coronary artery segment. The compliance of this bypass conduit must be sufficient to accommodate the high flow demands of systemic pressure with minimal pressure drop at the site of distal implantation [1].

Competitive flow occurs when the resistance of the coronary bypass graft closely matches that of the native coronary artery target [1, 2]. In this situation, both the native coronary artery and the bypass graft contribute to distal perfusion, each providing their own resistance to blood flow. For saphenous vein grafts, the pressures at the two ends of the circuit are identical, with only minor phasic variations, due to their large diameter and absence of muscular layers. In arterial grafts instead, due to the smaller diameter and higher vasomotor tone, the pressure at the proximal ostium is higher than at the distal anastomosis. Competitive flow between the native coronary artery and the arterial graft can result in further reductions of blood pressure through the conduit, which can cause the muscular layer to spasm and potentially close. This phenomenon has been widely reported in the literature [1, 3-5]. Given the near-universal use of the left internal thoracic artery (LITA) to graft the left anterior descending territory and the fact that current guidelines recommend the use of the right internal thoracic (RITA) and radial arteries (RA), the importance of the assessment of competitive flow should not be underestimated.

Current methods to estimate the severity of the coronary stenosis and the potential for competitive flow include visual inspection [6], [quantitative coronary angiography](#) [quantitative computerized angiography](#) (QCA) [7] and [fractional flow reserve](#) (FFR) [8]. [FFR is the only direct measurement method based on the hemodynamic effect of the stenosis in terms of reduction of blood flow capacity pressure ratios in order to determine the ischemic potential of the stenosis.](#) Several studies have shown that both visual inspection and QCA have poor correlation with FFR [9-13] and the 2018 European Guidelines for myocardial revascularization recommend that coronary artery lesions be measured with a FFR when evidence of ischemia is not available (Class I, Level of Evidence A) [14].

FFR evaluation, however, has not been widely adopted during the diagnostic workup of patients referred for surgical revascularization and only limited evidence exists on the role of preoperative FFR in patients undergoing coronary artery bypass surgery (CABG)

The Impact of Preoperative FFR on Arterial Bypass Graft flow rate (IMPAG) study was designed to evaluate the correlation between target vessel pre-operative FFR value and arterial graft functionality 6 months after surgery.

Methods

Study Design

We devised a prospective double-blind observational study performed in two different institutions in Belgium and Canada. The trial was registered (ClinicalTrials.gov Identifier: NCT02527044) and approved by the local research ethics boards in both institutions. All patients enrolled in the study provided written informed consent.

Outcomes

The primary outcome was the association between target vessel pre-operative FFR value and the anastomosis [flow rate function](#) at 6 months after surgery. Secondary outcome was the association between target vessel pre-operative FFR value and anastomosis occlusion at 6 months after surgery.

Study procedures

Patients were eligible for the study if they had multi-vessel coronary artery disease and were referred for isolated CABG using multiple arterial grafts. Patients were excluded if they had previous cardiac surgery, or were not candidate for the use of multiple arterial bypass grafts. The full list of eligibility criteria can be found in Supplementary Table 1. Patients were enrolled at the time of the diagnostic angiogram, or at the time of the pre-operative consultation with a cardiac surgeon.

Diagnostic angiography using either radial or femoral access was performed following the usual standard of care at each institution. FFR measurements of all major disease vessels were performed using a PressureWire Certus Agile Tip ([St. Jude Medical Abbott St. Jude at Minneapolis, Minnesota, Plymouth, MN](#)) with the use of intravenous adenosine as a hyperemic stimulus. FFR values were recorded by a study coordinator and blinded to the patient, interventional cardiologist, and surgeon.

The sequence and strategy of arterial revascularization was left to the operating surgeon. After surgery, all patients received therapies as recommended by the current American College of Cardiology and American Heart Association guidelines, including smoking cessation counseling and the administration of antiplatelet agents, beta blockers, lipid medications, and angiotensin converting enzyme inhibitors [15, 16].

Patients underwent follow-up angiography of all bypass grafts and anastomoses six months after surgery. Nitroglycerin (2 mg) was injected into each graft before filming. At least, two orthogonal views of each internal thoracic or radial artery graft imaging were obtained, with continued exposure as required to visualize distal runoff and the size of the target coronary bed. Angiographic evaluations were performed by 2

observers (one interventional cardiologist and one cardiac surgeon) blinded to the pre-operative FFR values. In the case of disagreement between observers, a third observer (interventional cardiologist) decided the value. Following a described method [3], [anastomotic graft functionality \(flow rate\)](#) was scored as 0 for an occluded graft, 1 when the flow from the native coronary artery was dominant, 2 when flow supply from the native coronary and from the graft was balanced, and 3 when the native coronary was fully opacified by the graft. A graft was considered “non functional” for scores of 0 to 2 and “functional” for score of 3. The coronary run off was graded using a semi quantitative scale based on the importance of the coronary bed beyond the area of the stenosis (A: excellent runoff, B: moderate runoff and, C: poor runoff).

Feasibility and Sample Size

A pilot phase was conducted to assess feasibility and allow sample size calculation. Twenty patients were recruited, and all patients had a follow-up angiogram six months after CABG. An average number of 3.8 FFR measurements and arterial anastomoses per patients was observed with no loss to follow up. Patients of the pilot phase were included in the full trial.

Sample size calculation was based on the results of the pilot phase and of a previously published trial [17]. We estimated a rate of 6-months graft failure of 5% in patients with positive FFR (>0.75) and 15% in patients with negative FFR (<0.75). With a power of 0.90 at an alpha level of 0.05, 414 anastomoses would be required to detect a statistically significant difference between groups. Assuming a 10% dropout rate, sample size was defined at 456 anastomoses. Based on the data of the pilot phase, 120 patients were deemed necessary.

An interim efficacy analysis was pre-established at 50% of the sample size. Due to the high level of statistical significance of the interim analysis, the Steering Committee decided to describe the results of the trial in the present report.

Analytic design and statistical analysis

Continuous variables were reported as mean and standard deviation while categorical variables were reported as count and percentage. The relationship between specific target FFR and degree of stenosis (DS) was investigated using linear regression and r^2 was used to quantify the degree of correlation between the two variables. Receiver operating characteristic (ROC) curves was used to identify the FFR and DS cut-off points with the highest discriminative power to predict non-functional anastomosis at 6-month angiography and the two variables were dichotomized accordingly. Areas under the ROC curves (AOC) was

used to compare the accuracy of FFR over the angiographic degree of stenosis (DS) to predict non-functional anastomosis. If 95%CI AUC lower limit was <0.5 the variable was considered not predictive.

Patient characteristics, graft configuration and target details including FFR and DS between functional and non-functional anastomoses were compared using t-test and chi-square test for continuous and categorical variable respectively. Variables associated with a P value $<.20$ were forced into mixed-effects longitudinal model with patient as the random effect to identify independent predictors of non-functional anastomoses. A stepwise selection based Akaike information criterion (AIC) was used to identify variables for the final model. The interaction between FFR and other target characteristics and graft configuration was further investigated using classification and regression trees method (CART).

Statistical analyses were performed using SPSS version 22.0 (IBM, Armonk, NY) and R software, version 3.2.3 (R Foundation). P-value < 0.05 was considered statistically significant.

Results

Overall 64 of 68 patients underwent the planned 6-month angiographic control. Mean angiographic follow up was 6.6 months (SD 0.9).

During the follow up period, 7 patients (10.2%) required 8 elective PCIs. Three patients had a RCA PCI due to distal RITA graft occlusion at a mean of 14.7 months post CABG. Three patients had a LAD PCI due to distal LITA occlusion at a mean of 7.3 months and one patient had a RCA and LAD PCI due to the occlusion of the RITA and the LITA after the sequential anastomosis at 5 months post CABG. There were no episodes of myocardial infarction or death.

From 64 patients, 199 anastomoses from 150 grafts were evaluated. There were 36 patients with double sequential and 7 patients with triple sequential grafts. The Y graft configuration was used in 172 anastomoses (86.4%).

The median percentage of DS was 70 (IQR:70-80) for LITA anastomoses, 80 (IQR:70-81.25) for RITA anastomoses and 82.5 (IQR:65-95) for RA anastomoses ($P=0.01$). Median FFR was 0.73 (IQR:0.67-0.80), 0.71 (IQR:0.65-0.75) for LITA anastomoses, 0.77 (IQR:0.69-0.82) for RITA anastomoses and 0.72 (IQR:0.64-0.84) for RA anastomoses ($P=0.001$).

Angiographic perfect patency rate was 85.2% for the LITA, 68.8% for the RITA and 76.7% for the RA anastomoses (P value for LITA vs RITA=0.052, LITA vs RA=0.38 and RITA vs RA=0.62). Forty-nine anastomoses were found to be non-functional (24%); of these, 27 (14%) were occluded, 13 (6%) presented a balanced flow and 9 presented reverse flow (4%). The proportion of functional anastomoses was 85.2% for the LITA, 68.8% for the RITA and 66.7% for the RA (P value for LITA vs RITA=0.01, LITA vs RA=0.16 and RITA vs RA=0.89).

Among the 49 anastomoses found to be non-functional, the preoperative target vessel FFR was significantly lower for those who required PCI ($n=8$) vs those who did not ($n=41$) (median/IQR 0.80/0.76-0.81 vs 0.83/0.81-0.89, $P=0.01$). Detailed description of the patients, the grafts and the anastomoses are given in Supplementary Tables 2-5.

Primary endpoint analysis

Preoperative FFR and angiographic DS presented a significant but very weak correlation ($R^2=3\%$, Figure 1). FFR but not DS were found predictive of non-functional anastomosis (FFR AUC 0.92; 95%CI 0.87-0.96 vs DS AUC 0.57, 95%CI 0.48-0.66; P value for comparison <0.001 ; Figure 2). FFR best cut off value was >0.78 with

a specificity of 0.78 and a sensitivity of 0.90 for non-functionality, while the DS best cut off value was <87.50 with a specificity of 0.20 and a sensitivity of 0.92 for non-functionality.

Table 1 compares patients, target and graft configuration between non-functional and functional anastomoses at 6-month angiogram. In non-functional anastomoses, the pre-operative FFR value was significantly higher than in functional anastomoses (0.83 ± 0.07 vs 0.66 ± 0.19 ; $P < 0.001$; Figure 3A-overall, 3B-per target, 3C-per conduit and Figure 4), while DS distribution did not differ between the two groups (73 ± 12 vs 76 ± 14 ; $P = 0.12$).

Anastomosis to the circumflex artery and posterior descending artery were more likely to be non-functional ($P = 0.02$). RITA and RA anastomosis were more likely to be non-functional when compared to LITA anastomosis ($P = 0.03$). At multivariable analysis (Table 2), $FFR < 0.78$ (OR 0.01; 95%CI 0-0.03; $P < 0.001$) and diabetes (OR 0.29; 95%CI 0.09-0.77; $P = 0.02$) were found to be associated with functional anastomosis while anastomosis to the posterior descending artery was associated with non-functional anastomosis (OR 5.09; 95%CI 1.22-22.17; $P = 0.02$). An $FFR < 0.70$ was associated with zero probability of non-functional anastomosis while this probability increased sharply when FFR values increased to, and surpassed 0.70 (Figure 5).

Recursive partitioning showed a non-functional anastomosis rate of 4% when $FFR \leq 0.78$; 32% when FFR was between 0.79 and 0.83 and the target vessel was the circumflex artery; 80% when FFR was 0.79 to 0.83 and the target was not the circumflex artery; and 87% when $FFR \geq 0.83$ (Figure 6).

Secondary endpoint analysis

FFR but not DS was found to be predictive of anastomosis occlusion (FFR AUC 0.86 95% CI: 0.78-0.93; vs DS AUC 0.59 95% CI: 0.49-0.70; P value for comparison < 0.001 ; Supplementary Figure 1). FFR best cut off value was > 0.78 with a specificity of 0.77 and a sensitivity of 0.92 for occlusion while the DS best cut off value was <87.50 with a specificity of 0.19 and a sensitivity of 0.92 for non-functionality.

Supplementary Table 6 compares patient demographics, target and graft configuration between occluded and non-occluded anastomoses at 6-month angiography. FFR but not DS was found to be significantly higher in non-functional anastomoses (0.83 ± 0.06 vs 0.68 ± 0.18 ; $P < 0.001$; Supplementary Figure 2A-overall, 2B-per target, 2C-per conduit) while DS distribution did not differ between the two groups (71 ± 11 vs 75 ± 14 ; $P = 0.11$).

At multivariable analysis (Supplementary Table 7), $FFR < 0.78$ (OR 0.02; 95%CI 0-0.08; $P < 0.001$) and use of the Y graft configuration (OR 0.20; 95CI 0.07-0.65; $P = 0.006$) were associated with patent anastomosis. Recursive partitioning showed an occluded graft rate of 3% when $FFR \leq 0.78$; 12% when $FFR > 0.78$ and the target was the circumflex artery and the number of sequential anastomosis was ≥ 2 ; 67% when $FFR > 0.78$

and target was other than circumflex artery; 86% when FFR ≥ 0.79 and target was the circumflex artery and the number of sequential anastomosis was < 2 (Supplementary Figure 3).

Discussion

We found a **highly**-significant association between the preoperative FFR measurement and anastomotic **flow rate function** in arterial bypass grafts 6 months after surgery. The best FFR cut-off value was 0.78 with less than 2% of the anastomosis to target vessel with preoperative FFR below this cut-off found to be non-functional at the follow-up angiogram.

The superiority of the arterial over venous graft is thought to result from favourable biological properties of the endothelium to protect this vessel against vasospasm, thrombus formation and atherosclerosis. In 2 previous studies we have demonstrated that the resistance in venous graft appears negligible and therefore the pressure at the distal graft anastomosis is nearly equal to the aortic pressure, minimizing risk of competition flow [1- 3]. In contrary, arteries are more likely to have a higher pressure drop leading to more competition flow.

FFR measurement has been validated as the most accurate invasive method of assessing the physiologic significance of a coronary artery stenosis [13]. This is reflected in studies such as the DEFER trial, which found that stenoses that were non-significant by FFR (≥ 0.75) were associated with a $<1\%$ risk of cardiac death or myocardial infarction whether or not they were stented [18]. Another key trial evaluating FFR was the FAME study, which found that FFR-guided PCI reduced the risk of death, repeat revascularization, and non-fatal myocardial infarction in the first year after the procedure [19]. Taken together, these prospective, randomized trials indicated clearly that FFR could identify lesions that warranted intervention, and that lesions that were not significant by FFR could safely be left alone. As a result of these trials, the use of FFR is supported by the professional guidelines, and has been widely adopted by interventional cardiologists during PCI.

However, FFR evaluation is not part of the standard assessment of CABG candidates and limited information on the role of FFR in cardiac surgery is available. Botman et al. examined the correlation between FFR measurement and graft patency, and found that grafting a stenosis with FFR >0.75 significantly increase the risk of graft occlusion ($p<0.0001$) [17]. Honda and colleagues evaluated the association between the preoperative FFR in the LAD and the intra-operative flow measured in the LITA-LAD graft and observed that FFR was positively correlated with graft flow, and systolic reverse flow [20]. The authors concluded that when a coronary lesion measured between 0.70 and 0.75 by FFR, there was a greater likelihood of competitive flow.

Fournier et al. performed a retrospective trial of 627 patients having at least one intermediate stenosis assessed as intermediate by either coronary angiography alone or angiography plus FFR [21]. The authors found that patients in the FFR-guided group had fewer anastomoses, and a lower rate of death and myocardial infarction 6 years after surgery (hazard ratio 0.59, 95% CI 0.38–0.93).

Of note, the recent Fractional Flow Reserve Versus Angiography Randomization for Graft Optimization (FARGO) trial [22] found that FFR-guided CABG had similar graft failure rates and clinical outcomes as angiography-guided CABG. Reasons for the difference compared to our findings are [probably likely](#) the low power of the FARGO trial (the study was prematurely stopped at 58% of the planned enrolment and angiographic control was available in only 74% of the enrolled sample) and the prevalent (67%) use of vein grafts (much less sensitive to competitive flow than arterial grafts). [A comparison between the two studies is provided in Table 4.](#) It is of note that in FARGO, there was a good correlation between the visual estimation of coronary artery stenosis and the FFR value, which contradicts our findings and most of the published literature [23].

Currently at least two prospective randomized trials are evaluating the role of FFR in CABG. The GRAFFITI trial [24], is a prospective, randomized, double-blind, multi-centre study examining the rate of occluded bypass grafts one year after surgery between angiographic versus FFR guided CABG. The FFR-Guided Percutaneous Coronary Intervention and CABG Surgery in patients with multivessel CAD (FAME) 3 Trial is a prospective, multicentre, randomized study with MACCE at 1 year as the primary outcome, and enrolment is ongoing [25]. The results of these trials will help to define the role of FFR in improving the outcome of CABG patients.

Our results suggest that preoperative FFR is associated with anastomotic arterial graft [flow rate function](#) at six months in CABG patients. Further studies are necessary to evaluate if the increase in angiographic functionality translates to improved clinical outcomes.

Limitations

The lack of a control group and the short follow-up are very important limitations. Even most importantly, this analysis was performed after inclusion of slightly more than 50% of the planned sample size so we cannot exclude that the study is underpowered and a type I error cannot be ruled out. However, the high level of significance for all the outcomes and the very narrow 95% CIs makes us confident in the solidity of our results. Also, the study was performed at two specialized care centres with expertise in performing both FFR and CABG with arterial grafts, and both the efficacy and safety results may not reflect the results in other centres and for surgeons using venous grafts. Finally, the study is obviously underpowered to detect

differences in clinical outcomes.

Conclusion

We describe a highly significant association between preoperative FFR and anastomotic arterial graft [flow rate function](#) at six months in CABG patients. These results suggest that FFR may play an important role in pre-operative planning of coronary artery bypass grafting procedures, and should be utilized whenever possible, particularly for surgeons utilizing multiple arterial conduits.

Figure Legends

Figure 1. Scatter plot between preoperative FFR and angiographic DS and linear regression line with 95%CI.

Figure 2. Receiver operating characteristic (ROC) curves to compare accuracy of FFR and DS in predicting non-functional anastomosis at 6-month angiography

Figure 3. Sinaplot conveying information of both the number of data points, the density distribution, outliers of FFR value in non-functional vs functional anastomosis at 6 month-angiography.

Figure 4. Distribution of preoperative FFR according to anastomosis functionality at 6-month angiography.

Figure 5. Predicted probability of anastomosis non-functionality obtained from multivariable logistic model.

Figure 6. Numbers in each box indicate proportion of non-functional grafts and percentage of anastomoses (on overall sample size) in each FFR category.

Supplementary Figure 1. Receiver operating characteristic (ROC) curves to compare accuracy of FFR and DS in predicting occluded anastomosis at 6-month angiography

Supplementary Figure 2. Sinaplot conveying information of both the number of data points, the density distribution, outliers of FFR value in occluded vs non-occluded anastomosis at 6 month-angiography.

Supplementary Figure 3. Numbers in each box indicate proportion of occluded grafts and percentage of anastomoses (on overall sample size) in each FFR category.

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	Non-Functional (n = 49)	Functional (n = 150)	P value
Age	66.98 (10.98)	65.37 (10.35)	0.35
Dyslipidemia	37 (75.5)	120 (80.0)	0.64
Diabetes	13 (26.5)	63 (42.0)	0.07
Smoking	22 (44.9)	69 (46.0)	1.000
Renal insufficiency	4 (8.2)	4 (2.7)	0.20
Previous MI	11 (22.4)	40 (26.7)	0.69
LV Ejection fraction	64.92 (14.10)	62.03 (10.55)	0.12
Prior PCI	10 (20.4)	46 (30.7)	0.22
Angiographic stenosis	72.45 (11.73)	75.77 (13.66)	0.12
FFR	0.83 (0.07)	0.66 (0.19)	<0.001
Y graft	41 (83.7)	131 (87.3)	0.68
<u>Target vessel</u>			0.01
<i>CX</i>	23 (46.9)	54 (36.0)	
<i>DIA</i>	2 (4.1)	20 (13.3)	
<i>LAD</i>	10 (20.4)	53 (35.3)	
<i>PDA</i>	14 (28.6)	23 (15.3)	
Target vessel diameter	1.83 (0.37)	1.94 (1.93)	0.67
<u>Conduit</u>			0.02
<i>LITA</i>	12 (24.5)	69 (46.0)	
<i>RA</i>	3 (6.1)	6 (4.0)	
<i>RITA</i>	34 (69.4)	75 (50.0)	
Sequential graft	16 (32.7)	54 (36.0)	0.80

Number of sequential anastomoses	1.41 (1.06)	1.01 (1.11)	0.03
SYNTAX score	21.12 (6.59)	22.93 (6.83)	0.10
Off pump surgery	43 (87.8)	115 (76.7)	0.14

Continuous data are presented as mean and

(standard deviation). Categorical data as number and (percentage)

Table 1. Patients and operative characteristics for non-functional vs functional anastomosis at 6 months follow-up.

		Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
		<i>Enter model</i>			<i>Stepwise</i>		
Diabetes		0.23	0.06-0.79	0.01	0.26	0.09-0.77	0.01
LV EF		1.00	0.95-1.05	0.99			
DS>87.5%		0.51	0.07-3.82	0.51			
FFR<0.78		0.01	0.00-0.03	<0.0001	0.01	0.00-0.03	<0.0001
N of sequentials		0.75	0.24-2.34	0.62			
Target	<i>CX</i>	Ref					
	<i>DIA</i>	2.72	0.08-93.10	0.57	1.38	0.11-16.88	0.80
	<i>LAD</i>	6.31	0.30-132.62	0.23	3.80	0.86-16.81	0.07
	<i>PDA</i>	4.69	1.02-21.55	0.04	5.09	1.22-21.17	0.02
Conduit	<i>LITA</i>	Ref					
	<i>RA</i>	10.68	0.21-532.10	0.23			
	<i>RITA</i>	2.80	0.07-116.92	0.58			
Off pump		3.82	0.85-17.25	0.08	3.20	0.84-12.27	0.08
SYNTAX score		0.97	0.89-1.06	0.51			

Table 2. Multivariable analysis for non-functional anastomosis at 6 month angiography.